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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,226	06/29/2001	Eric J. Benjamin	AM100155	9422
25291	7590	11/06/2006	EXAMINER	
WYETH PATENT LAW GROUP 5 GIRALDA FARMS MADISON, NJ 07940			KANTAMNENI, SHOBHA	
			ART UNIT	PAPER NUMBER
			1617	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/896,226

Applicant(s)

BENJAMIN ET AL.

Examiner

Shobha Kantamneni

Art Unit

1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 07 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 32-42 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) NONE is/are allowed.
- 6) ☒ Claim(s) 32-42 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>08/07/06</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

This Office Action is a response to Applicant's response filed on 08/07/2006 wherein no amendment is filed, i.e., no claims are amended, cancelled, or newly submitted.

The rejection of claims 32-42 under the judicially created doctrine of obviousness type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,479,535 is MAINTAINED. Note that applicants will file a terminal disclaimer upon indication of allowable claims.

Applicant's arguments have been considered, but not found persuasive, the rejection of claims 32-42 under 35 U.S.C. 103(a) as being unpatentable over Raveendranath et al. (WO 9919293, PTO-1449 submitted September 18, 2001), in view of Sawicka (Pharmazie 1991, vol.46 page 519-521, PTO-1449 submitted September 28, 2001), and further in view of Gibson et al. (US 5,811,120, PTO-892) is MAINTAINED. See under Response to Arguments.

Applicant's arguments have been considered, but not found persuasive, the rejection of claims 32-42 under 35 U.S.C. 103(a) as being unpatentable over Miller et al. (EP 802183, PTO-1449 submitted June 10, 2005), in view of Sawicka (Pharmazie 1991, vol.46 page 519-521, PTO-1449 submitted September 28, 2001), and further in view of Gibson et al. (US 5,811,120, PTO-892) is MAINTAINED. See under Response to Arguments.

Currently claims 32-42 are pending.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 32-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raveendranath et al. (WO 9919293, PTO-1449 submitted September 18, 2001), in view of Sawicka (Pharmazie 1991, vol.46 page 519-521, PTO-1449 submitted September 28, 2001), and further in view of Gibson et al. (US 5,811,120, PTO-892).

Raveendranath et al. disclose a pharmaceutical composition comprising the instant particular compound, 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxyl)-benzyl]-1H-indol-5-ol (see its structure at the bottom of page 37 and Example 15 at page 40 and a pharmaceutically acceptable carrier or excipients to be administered to a mammal; the testing results for the composition comprising Example 15 at page 42, 44, 46, 47 are also disclosed. Raveendranath et al. also disclose that the effective amount of the compound to be administered for treating diseases therein is a dose of from about 0.1 mg/day to about 1,000 mg/day; preferably, administration will be from about 50 mg/day to about 600 mg/day in a single dose or in two or more divided doses (see page 29, lines 23-25).

In particular, Raveendranath et al. teach that: "Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms including tablets, capsules, buccal, forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioa starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums. etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compounds." (emphases added, see page 30, lines 1-19).

Raveendranath et al. does not expressly disclose the pharmaceutical composition herein further comprising an antioxidant.

Raveendranath et al. do not expressly disclose the specific range of amounts of a filler and disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition herein.

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Sawicka teaches that adding an antioxidant to a pharmaceutical composition is well known in the art and the stability of a pharmaceutical formulation may be increase by antioxidant addition. See abstract and the entire article.

Gibson et al. (US 5,811,120, PTO-892) teaches a pharmaceutical composition and a process for making such composition comprising a poorly soluble pharmaceutical agent, raloxifene hydrochloride salt. It is also taught that poor or low water solubility, and hydrophobicity of raloxifene salt results in limited bioavailability, optimum, and consistent absorption. See abstract; column 1, lines 55-64. The pharmaceutical composition also comprises surfactant or wetting agents, disintegrants, lubricants, glidants, and water soluble diluents. Surfactants or wetting agents such as sodium laurylsulfate, cholic acid, polyoxyethylene sorbitan fatty acids esters, etc are disclosed. See column 3 line 60-column 4, line 2; see Formulation 6, wherein 2 % of sodium lauryl sulfate is present. Disintegrants such as starches, clays, celluloses, sodium starch glycolate are disclosed. See column 4, lines 8-15; see Formulation 9, wherein 5.8 % of sodium starch glycolate is present. Lubricants or glidants such as 0.4 % magnesium stearate (see Formulation 9, column 8), colloidal silicon dioxide, microcrystalline cellulose, sodium lauryl sulfate etc. are taught. See column 4, lines 16-26. The composition also contains water soluble diluents such as about 37 % lactose, sucrose etc. See column 4, lines 3-8; see Formulation 6. The compositions for oral administration may be in the form of tablets, capsules. See Formulations 1-15.

It would have been obvious to a person of ordinary skill in the art at the time of invention to add an antioxidant to the composition of Raveendranath et al. One of

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ordinary skill in the art at the time of invention would have been motivated to add an antioxidant to the pharmaceutical composition of Raveendranath et al. with the expectation of increasing the stability of the composition since adding an antioxidant to a pharmaceutical composition to increase stability is well known in the pharmaceutical art.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine the specific range of amounts of a filler and disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition herein.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine the specific range of amounts of a filler, disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition with the expectation of obtaining a pharmaceutical composition with increased solubility, and optimum bioavailability of 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol because Gibson teaches such specific range of amounts of a filler, disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition comprising low soluble, hydrophobic compound.

Further, the determination and the optimization of amounts of known active agents, excipients such as a known filler, known disintegrant components, a known wetting agent, a known lubricant, and a known glidant in a pharmaceutical composition are considered conventional to an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly *prima facie* obvious over the combined teachings of the prior art.

Claims 32-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al. (EP 802183, PTO-1449 submitted June 10, 2005), in view of Sawicka (Pharmazie 1991, vol.46 page 519-521, PTO-1449 submitted September 28, 2001), and further in view of Gibson et al. (US 5,811,120, PTO-892).

Miller et al. disclose a pharmaceutical composition comprising the instant particular compound, 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxyl)-benzyl]-1H-indol-5-ol (see its structure Example No. 97, at the bottom of page 8; page 37-38; page 41, line 55) or 1-[4-(2-Azepan-1-yl-ethoxyl-benzyl)-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (see its structure Example No. 98: page 37-38; page 44, lines 17-27) and a pharmaceutically acceptable carrier or excipients to be administered to a mammal. The testing results for the composition comprising Example 97 and 98 at page 64, 72, 74, 46, 47 are also disclosed. Miller et al. also disclose that the effective amount of the compound to be administered for treating diseases therein is a dose of from about 0.1 mg/day to about 1,000 mg/day; preferably, administration will be from about 50 mg/day to about 600 mg/day in a single dose or in two or more divided doses (see page 13, lines 16-18).



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In particular, Miller et al. teach that:

"Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms including tablets, capsules, buccal, forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums. etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may be utilize standard delay or time release formulations to alter the absorption of the active compounds." (emphases added, see page 13, lines 25-37).

Miller et al. does not expressly disclose the pharmaceutical composition herein further comprising an antioxidant.

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Miller et al. do not expressly disclose the specific range of amounts of a filler, disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition herein.

Sawicka teaches that adding an antioxidant to a pharmaceutical composition is well known in the art and the stability of a pharmaceutical formulation may be increase by antioxidant addition. See abstract and the entire article.

Gibson et al. (US 5,811,120, PTO-892) teaches a pharmaceutical composition and a process for making such composition comprising a poorly soluble pharmaceutical agent, raloxifene hydrochloride salt. It is also taught that poor or low water solubility, and hydrophobicity of raloxifene salt results in limited bioavailability, optimum, and consistent absorption. See abstract; column 1, lines 55-64. The pharmaceutical composition also comprises surfactant or wetting agents, disintegrants, lubricants, glidants, and water soluble diluents. Surfactants or wetting agents such as sodium laurylsulfate, cholic acid, polyoxyethylene sorbitan fatty acids esters, etc are disclosed. See column 3 line 60-column 4, line 2; see Formulation 6, wherein 2 % of sodium lauryl sulfate is present. Disintegrants such as starches, clays, celluloses, sodium starch glycolate are disclosed. See column 4, lines 8-15; see Formulation 9, wherein 5.8 % of sodium starch glycolate is present. Lubricants or glidants such as 0.4 % magnesium stearate (see Formulation 9, column 8), colloidal silicon dioxide, microcrystalline cellulose, sodium lauryl sulfate etc. are taught. See column 4, lines 16-26. The composition also contains water soluble diluents such as about 37 % lactose, sucrose

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etc. See column 4, lines 3-8; see Formulation 6. The compositions for oral administration may be in the form of tablets, capsules. See Formulations 1-15.

It would have been obvious to a person of ordinary skill in the art at the time of invention to add an antioxidant to the composition of Raveendranath et al. One of ordinary skill in the art at the time of invention would have been motivated to add an antioxidant to the pharmaceutical composition of Raveendranath et al. with the expectation of increasing the stability of the composition since adding an antioxidant to a pharmaceutical composition to increase stability is well known in the pharmaceutical art.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine the specific range of amounts of a filler and disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition herein.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine the specific range of amounts of a filler, disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition with the expectation of obtaining a pharmaceutical composition with increased solubility, and optimum bioavailability of 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-ylethoxy)-benzyl]-1H-indol-5-ol because Gibson teaches such specific range of amounts of a filler, disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition comprising low soluble, hydrophobic compound.

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Further, the determination and the optimization of amounts of known active agents, excipients such as a known filler, known disintegrant components, a known wetting agent, a known lubricant, and a known glidant in a pharmaceutical composition are considered conventional to an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly *prima facie* obvious over the combined teachings of the prior art.

### ***Response to Arguments***

Applicants argues that "One skilled in the art would not be motivated to first select, then combine the teachings of each of Raveendranath and Miller with respect to indol compounds with the teachings of Gibson '120 with respect to the use of a wetting agent and glidants in benzothiophene. Those of skill in the art would have no reason to look to Gibson '120 since Raveendranath and Miller, individually, provide guidance as to suitable pharmaceutical formulations for the indol compounds. Even if one were interested in altering these formulations, one of skill in the art would not look to Gibson '120 because it is limited to benzothiophenes rather than to the indols as claimed by Applicants. One skilled in the art would not have any reason to expect that the advantages of the wetting agent and glidants in the raloxifene formulations would be

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seen in indol formulations.” These arguments have been fully considered, but not found persuasive because Raveendranath et al., and Miller et al. teaches that the compositions therein containing indol compounds are formulated with wetting agents such as sodium lauryl sulfate, and glidants such as magnesium stearate. Raveendranath et al., and Miller et al. do not teach the specific amounts of glidants, and wetting agents as in the instant claims. Gibson et al. teaches that raloxifene hydrochloride which contains benzothiophene, two phenolic hydroxyl groups has low solubility in water, which limits its bioavailability. Gibson teaches that raloxifene in combination with a hydrophilic carrier composition which contains surfactant, binder, lubricant has increased solubility. Gibson also teaches such specific range of amounts of a wetting agent, and a glidant as instantly claimed in a pharmaceutical composition comprising low soluble, hydrophobic compound such as raloxifene. It would have been obvious from the teachings of Gibson et al. to employ specific amounts of wetting agents, glidants etc. in the composition taught by Raveendranath et al., and Miller et al. because 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxyl)-benzyl]-1H-indol-5-ol, which has two phenolic hydroxyl groups, and significantly similar structure (indole and benzothiophene are closely related heterocyclic aromatic compounds), and similar substituents as raloxifene, would be expected to have similar solubility in water as raloxifene. One having ordinary skill in the art at the time of the invention would have been motivated to employ the specific range of amounts of a filler, disintegrant components, a wetting agent, a lubricant, and a glidant in a pharmaceutical composition with reasonable expectation of obtaining a pharmaceutical composition with increased

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solubility, and optimum bioavailability of 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxyl)-benzyl]-1H-indol-5-ol because Gibson teaches that solubility of low soluble, hydrophobic compound, containing 2 phenolic hydroxyl is increased in the compositions therein.

Further, it has been held that it is within the skill in the art to select optimal parameters, such as amounts of known ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

### ***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-

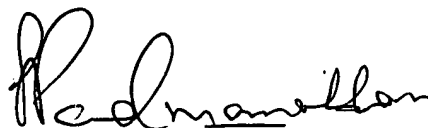
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272-2930. The examiner can normally be reached on Monday-Tuesday, and Thursday-Friday, between 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni, Ph.D  
Patent Examiner  
Art Unit : 1617



**SREENI PADMANABHAN**  
**SUPERVISORY PATENT EXAMINER**